Editorial

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Managing periprocedural thrombocytopenia in cirrhosis: Aiming for a safety window

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Among the challenges that care of patients with cirrhosis brings, management of periprocedural bleeding risk is a common concern as chronic liver disease (CLD) implies the need for frequent invasive diagnostic and therapeutic procedures, such as biopsies, variceal band ligation or percutaneous ablation of hepatocellular carcinoma.

In this issue of the *Journal of Hepatology*, Terrault *et al.* report the results of a phase II multicentre, randomized, placebo-controlled study of a 7-day pre-procedural administration of avatrombopag, a second-generation thrombopoietin receptor agonist in patients with cirrhosis and thrombocytopenia (<58,000/μl) [1]. Most interventions consisted of dental procedures and gastrointestinal endoscopies. Two formulations of avatrombopag were tested in two separate cohorts. Patients received one of the five doses of the drug or placebo. The primary end point was an increase of at least 20,000/μl platelets from baseline and a total platelet count over 50,000/μl between days 4 and 8 after the first dose. Overall, 48% of patients receiving the study drug reached this end point *vs.* 8% in the placebo group. The level of increase of the platelet count was highest with the highest dose administered. Transfusion of platelets was not a study end point and not standardized across study sites; therefore no conclusion could be drawn about this aspect. There was no difference in total or serious adverse events between patients treated with avatrombopag and those receiving placebo. Yet, one patient receiving the first-generation formulation of avatrombopag at the highest dose (100/80 mg) was found to have a portal vein thrombosis (PVT) after having reached a maximal platelet count of 199,000/μl.

Moderate degrees of thrombocytopenia in CLD are not associated with increased bleeding, presumably because platelet aggregation is preserved as a consequence of increased levels of circulating von Willebrand factor and decreased activity of its cleaving protease, ADAMTS13 [2,3]. However, for more profound degrees of thrombocytopenia, the risk of bleeding increases. On top of their role in primary haemostasis (platelet aggregation), platelets also contribute to secondary haemostasis (coagulation). Indeed, thrombin generation in the presence of thrombomodulin decreases together with platelet counts in patients with cirrhosis [4]. This appears to be especially true when the platelet count is below 60,000/μl. Conversely, when platelet numbers are adjusted to those of controls, the plasma of patients with cirrhosis generates equal amounts of thrombin. This effect may involve the phospholipid surface that platelets provide for the activation of the prothrombinase complex. A clear threshold of platelet counts, below which the bleeding risk clearly increases, cannot be proposed, but the following data provide some insight. In patients from the HALT-C trial, 75% of liver biopsy-related haemorrhages occurred in patients with platelet counts below 60,000/μl [5]. In an Italian study, analysing bleeding events after common diagnostic and therapeutic interventions in 125 patients with cirrhosis and thrombocytopenia, bleeding occurred in 32% of those with platelet counts below 75,000/μl, compared to none of those with platelet counts between 75 and 150,000/μl [6]. The platelet count was a better predictor of bleeding than the international normalized ratio (INR).

Thrombocytopenia in cirrhosis is of multifactorial origin (Fig. 1), resulting from splenic sequestration of platelets, increased destruction of platelets within the spleen, intrasplenic production of autoantibodies, plasma expansion resulting in haemodilution and decreased activity of thrombopoietin [7]. The liver is an important site of thrombopoietin production. Levels of circulating thrombopoietin, as well as those of messenger RNA in hepatocytes, are decreased in patients with cirrhosis and are restored in the weeks following liver transplantation [8–10].

This study by Terrault *et al.* is important because it is the first published experience of the second-generation thrombopoietin receptor agonist avatrombopag in patients with CLD and paves the way for a larger, phase III trial. Experience from the first-gen-

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Abbreviations: CLD, chronic liver disease; PVT, portal vein thrombosis; INR, international normalized ratio.

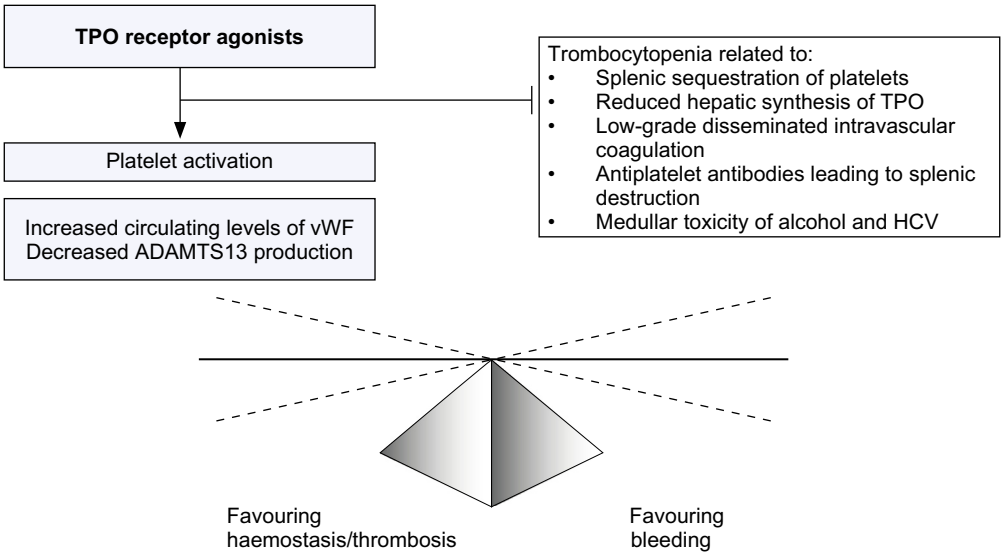

Fig. 1. Changes in primary haemostasis in patients with chronic liver disease. TPO receptor agonists not only increase platelet counts but also enhance platelet activation and function. The balance between thrombosis and bleeding is fragile in chronic liver disease patients. HCV, hepatitis C virus; TPO, thrombopoietin; vWF, von Willebrand Factor.

eration thrombopoietin receptor agonists, romiplostim and eltrombopag, in patients with CLD warrants a note of caution. Romiplostim, a parenteral thrombopoietin analogue administered weekly, seemed promising in raising platelet counts before elective minor surgeries (mostly cataract, hernia and fracture fixation) in patients with Child-Pugh C hepatitis C-related cirrhosis and severe thrombocytopenia (<50,000/μl) in a small single-centre, single-arm, open-label Egyptian study [11]. In the ELEVATE trial, 292 patients with thrombocytopenia (<50,000/μl) and CLD were randomized to receive eltrombopag or placebo for 14 days before an invasive procedure, again mostly dental or endoscopic [12]. The drug avoided platelet transfusions in a large number of patients (72% *vs.* 19%). However, PVT developed in 4% of patients in the eltrombopag group as compared to 1% in the placebo group. This finding led to the early termination of the trial. Eltrombopag has also been tested in patients with hepatitis C-related cirrhosis and thrombocytopenia to increase platelet counts and permit interferon-based therapy. In a first placebo-controlled study of 72 patients with platelet counts between 20,000 and 70,000/μl, 75% to 95% of patients treated with different doses of eltrombopag for 4 weeks reached platelet counts over 100,000/μl and initiated interferon treatment, compared to none in the placebo group [13]. Adverse events were comparable between groups. In the larger ENABLE-1 and 2 trials, 1520 patients with baseline thrombocytopenia (<75,000/μl) infected with hepatitis C virus and candidates for pegylated interferon therapy received eltrombopag or placebo during antiviral treatment after a documented response to eltrombopag [14]. The use of eltrombopag, when compared with placebo, permitted higher doses of interferon and was associated with higher sustained virological response rates (23% *vs.* 14%, $p = 0.0064$ in ENABLE-1 and 19% *vs.* 13%, $p = 0.0202$ in ENABLE-2). However, a significantly higher incidence of thromboembolic events was observed in the eltrombopag group (3% *vs.* 1%). One third of these events were PVT. Importantly, hepatic decompensation occurred twice more commonly in patients receiving eltrombopag. This result is in line with the beneficial effect of anticoagulation and antiplatelet drugs on liver fibrosis in animal models [15], and with the protective effect of prophylactic doses of enoxaparin on liver decompensation in patients with cirrhosis [16].

The other indication for the use of thrombopoietin receptor agonists is refractory idiopathic thrombocytopenic purpura. A meta-analysis of currently available randomized controlled trials comprising 1180 patients described a statistically non-significant trend towards an increased thromboembolic risk [17]. The thrombotic risk associated with thrombopoietin receptor agonists could even be higher in CLD patients than in those without liver disease. The efficacy of thrombopoiesis, generated by thrombopoietin receptor agonists, in CLD patients could be one of the factors responsible for the increased thrombotic risk. In the ELEVATE trial, 5 of the 6 patients with PVT had a maximal platelet count over 200,000/μl. In the study by Terrault *et al.*, the maximal platelet count recorded in the patient with PVT was 199,000/μl. Splenic sequestration of platelets in CLD yields lower total platelet counts and may lead to underestimation of the thrombopoiesis, generated by these drugs. Other factors, including decreased portal blood flow and hypercoagulability, associated with cirrhosis, may synergize with the increase in platelet counts, due to thrombopoietin receptor agonists to promote portal vein thrombosis in CLD patients [4,18].

It is now widely recognized that haemostasis in patients with CLD is "rebalanced" [19]. Studies concerning the use of thrombopoietin receptor agonists have demonstrated that this rebalance is fragile and that a tendency to bleed can easily be shifted to a tendency to clot in the individual patient. Thrombopoietin receptor agonists, including avatrombopag, raise platelet counts in a dose-dependent manner. Important questions remain to be answered before thrombopoietin receptor agonists can be safely used in patients with cirrhosis: (a) How can the procedure-related bleeding risk in individual patients be better predicted? (b) What is the safety window in platelet counts, induced by thrombopoietin receptor agonists, to reduce the bleeding risk without exposing the patient to thrombosis? (c) Is the risk of liver decompensation really increased with elevated platelet counts or

other effects of thrombopoietin receptor agonists? (d) What are the risk factors for developing PVT or liver decompensation in patients receiving thrombopoietin receptor agonists? Hopefully, the ongoing phase III randomized placebo-controlled trial of avatrombopag prior to an invasive procedure in patients with CLD and platelet counts below 50,000/μl (National Clinical Trials identifiers NCT01976104 and NCT01972529) will bring elements of answer.

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Conflict of interest

P.-E. Rautou is an investigator for Eisai. The other authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

J. Bissonnette and P.E. Rautou drafted the manuscript. D. Valla critically revised the manuscript.

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